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(21)出願番号 特願平4-43363	(71)出願人 000002901 ダイセル化学工業株式会社 大阪府堺市鉄砲町1番地
(22)出願日 平成4年(1992)2月28日	(72)発明者 岡本 佳男 愛知県名古屋市東区矢田町2-66-222
	(72)発明者 八島 栄次 愛知県名古屋市名東区亀ノ井2-38-409
	(74)代理人 弁理士 古谷 鑑 (外3名)

(54)【発明の名称】 光学分割膜及びそれを用いた光学分割方法

(57)【要約】

【構成】 基材膜の内部及び両面に、多糖誘導体等の光学分割能を有する物質を固着させた光学分割膜の片面にラセミ体原液を接触させた後、他面を洗浄液で洗浄することにより光学活性体を得る。

【効果】 操作が容易であり、大容量処理に適している事から経済的であり、複雑な化学構造式を持つ $\beta$ プロッカー等の医農薬についても、直接分割によって光学活性体が得られる。

## 【特許請求の範囲】

【請求項1】 基材膜の内部及び両面に光学分割能を有する物質を固着させてなる光学分割膜。

【請求項2】 光学分割能を有する物質が多糖誘導体である請求項1記載の光学分割膜。

【請求項3】 請求項1又は2記載の光学分割膜の片面にラセミ体原液を接触させた後、他面を洗浄液で洗浄することにより光学活性体を得ることを特徴とする光学分割方法。

## 【発明の詳細な説明】

## 【0001】

【産業上の利用分野】 本発明は光学異性体の分割用膜とその膜を用いた光学分割方法に関するものである。特に現在医薬として抗不整脈、抗狭心症、降圧薬や、緑内障の治療に適用されている $\beta$ -ブロッカー類の光学分割にも効率的な分割を可能にする新規な膜、及びその膜を用いた光学分割方法に関するものである。

## 【0002】

【従来の技術及び発明が解決しようとする課題】 医薬、香料、調味料、液晶などの分野で研究開発の進展に伴い益々光学活性体の重要性が高まっている。特に生命現象において光学活性体が特異な働きをし、生理活性上光学活性体の一方(D体又はL体あるいは+体又は-体)を得ることが非常に有用な場合が多いことが知られている。厚生省は1985年版医薬品製造指針において「当該薬物がラセミ体である場合にはそれぞれの異性体について吸収、分布、代謝、排泄動態を検討しておく事が望ましい」と記載している。

【0003】 光学活性体をラセミ体から得る工業的手法としては、現在、ジアステレオマー法、優先晶出法、酵素法、クロマトグラフィー法などがある。ジアステレオマー法はラセミ体に光学活性な酸又は塩基(分割剤)を作用させ、生成したジアステレオマー塩の溶解度の差を利用して分別結晶を行い、再結晶を行うことにより精製したのち化学的処理により分解することによって光学活性体を得る方法である。この方法においては分割剤がラセミ体と容易に塩又は誘導体を形成するものでなければならぬことによる分割剤選択の困難さが付随する。更に溶解度差が小さいかあるいは無い場合には光学分割が不可能である。又、高純度の光学活性体を得るのも困難である等の問題点を有している。

【0004】 優先晶出法はラセミ体の過飽和溶液に一方の対掌体の純粋な結晶を種として加え、これと同種の対掌体の結晶のみを選択的に成長させ析出させる方法である。非常に優れた方法であるにも拘らず、次のような課題があるために広範囲に活用されているとはいひ難いのが実状である。即ち、あるラセミ体を優先晶出法で分割しようとするには、先ずラセミ体と両活性体の溶解度を測定し、ラセミ体>活性体であること、又融点は活性体の方がラセミ体より高いこと、更にラセミ体の飽和溶液

には活性体が溶解しないこと、などを事前に確認しておく必要がある(山中宏、田代泰久、季刊化学総説、No.6、1989年、4~5ページ)。

【0005】 酵素を用いる光学分割法は「発酵法」と「酵素法」に分別できるが、酵素はL-アミノ酸がペプチド結合してできた一種の不斉分子であるため多くの場合反応は不斉反応として進行する。即ち、酵素自身が触媒として高度な選択性をもつため、光学活性体の生産の場合において利用され、光学活性体を大量に得る方法として適しており、例えば、ヒダントイナーゼ反応と化学的脱カルバミル化反応を組み合わせた酵素法によるD-アミノ酸の工業的生産技術が確立している[S.TAKAHASHI, "Biotechnology of Aminoacid Production", H.YAMADA et al (eds), Kodansha Ltd. (1986) p269]。また米国特許第4,800,162号ではポリアクリロニトリル系中空糸膜内に酵素を固定化し、光学活性体を得る方法が記載されている。しかし、酵素法における問題点は光学分割をしたいラセミ化合物に適合する酵素を見つけるのが非常に困難なことである。

【0006】 クロマトグラフィー法はキラルな化合物を充填剤として用い固定相とし、移動相中の光学異性体との相互作用による移動相の分布の差を利用して分離する方法である。最近のHPLC(高速液体クロマトグラフィー)用充填剤の開発はめざましいものがあり、光学分割用カラムが多数上市されるとともにかなり大量の分取も行われる状況に至っているが、工業的規模で経済的に行われる域には今一步といったところである。

【0007】 一方、膜分離法は海水淡水化をめざす逆浸透膜の技術開発が約30年前に飛躍的な進展を遂げたのを契機にして精密濾過膜や限外濾過膜もほぼ並行して技術開発が進められ、いわゆる人工膜が実用技術として定着し、医薬、電子工業、自動車等あらゆる産業分野で活用されている。これらの膜は基本的には分子サイズと膜の孔径との相対的な差を利用した分子篩の原理に基づいて分離が行われており、光学異性体のように分子量も同じ、化学的・物理的特性も異なるものの分離には全く不向きであることは周知のことである。

【0008】 膜分離法の特徴は大量の処理に適していることと分離コストが安い事である。従って光学分割に適した膜の開発とその膜を旨く使いこなす技術の開発が大きく要望されることになっている。特に被分割ラセミ体を化学修飾なしに直接膜法で光学活性体に分割できればその技術の工業的価値は素晴らしいといえる。即ち、このような膜を用いて光学活性体を分離する方法は、上述のようなジアステレオマー法、優先晶出法、酵素法、クロマトグラフィー法等がそれもつ固有の欠点を克服する新規な技術であり、大量の光学活性体が経済的に得られることが期待できる。

【0009】 膜を用いた光学活性体の分離については、すでに、膜材料に光学活性な物質を導入して得られる膜

を用いる分離法（特願平2-229743号）や、 $\alpha$ -ヘリックス構造を持つポリアミノ酸を構成成分とするポリマーからなる膜を用いる分離法（特願平2-334352号）の如き技術や、クラウン化合物をポリプロピレン製精密濾過膜に保持させた液膜による分離法（特公昭63-57083号）等が知られている。しかし、これらはいずれもアミノ酸を対象とした膜であって複雑な化学式を示す医薬等の分離に適用されるものではない。従って、本発明の課題は、医薬等を効率的に光学分割できる膜、及びその膜を用いた分離法を提供することにある。

## 【0010】

【課題を解決するための手段】本発明者は上記課題を解決すべく銳意研究の結果、すでに光学異性体の分析や分取において液体クロマトグラフィーのカラム充填剤に多用されている多糖誘導体等の光学分割能を有する物質に着目し、これを基材膜の内部及び両面に固着することによって、良好な分割能を有する光学分割膜が得られることを見出し本発明を完成了した。即ち、本発明は、基材膜の内部及び両面に、多糖誘導体等の光学分割能を有する物質を固着させてなる光学分割膜、及びこの光学分割膜の片面にラセミ体原液を接触させた後、他面を洗浄液で洗浄することにより光学活性体を得ることを特徴とする光学分割方法を提供するものである。

【0011】本発明において、光学分割能を有する物質を基材膜の内部及び両面に固着させる方法としては、光学分割能を有する物質を有機溶媒に溶解（ドープという）したのちこれを膜の片面あるいは両面にコーティングする方法や、溶解ドープ中に膜を浸漬する方法等があるが、本発明の場合はどうらの方法をとってもその効果は変わらない。

【0012】本発明に用いられる光学分割能を有する物質としては、多糖誘導体が好ましい。多糖としては、合成多糖、天然多糖を問わず、例えば $\beta$ -1,4-グルカン（セルロース）、 $\alpha$ -1,4-グルカン（アミロース、アミロベクチン）、 $\alpha$ -1,6-グルカン（デキストラン）、 $\beta$ -1,6-グルカン（ブスツラン）、 $\beta$ -1,3-グルカン、 $\alpha$ -1,3-グルカン、 $\beta$ -1,2-グルカン、 $\beta$ -1,4-ガラクトン、 $\beta$ -1,4-マンナン、 $\alpha$ -1,6-マンナン、 $\beta$ -1,2-フラクトン（イヌリン）、 $\beta$ -1,4-キシラン、 $\beta$ -1,3-キシラン、 $\beta$ -1,4-キトサン、キチン、アガロース等が挙げられる。特に好ましいのは高純度の多糖が容易に得られるセルロース、アミロース等である。本発明に用いられる多糖誘導体としては、上記多糖のエステル誘導体、ガルバメート誘導体、エーテル誘導体等があり、そのいずれであっても構わない。

【0013】又、本発明に用いられる基材膜は限外濾過膜、精密濾過膜、微多孔膜が使用され得る。その素材としては酢酸セルロース、硝酸セルロース、再生セルロース、テフロン、ポリプロピレン、ポリエチレン、ポリサ

ルホン、ポリエーテルサルホン、ポリスチレン、ポリアミド、ポリイミド、ポリアクリロニトリル等で、被分割化合物を溶解する溶媒に溶解しない素材で作られたものならいずれの素材で作られた膜も適用可能である。

【0014】膜に多糖誘導体を固着させる為に多糖誘導体を有機溶媒に溶解させてドープをつくるが、それに使用される溶媒としては、ジメチルホルムアミド(DMF)、ジメチルスルホキシド(DMSO)、テトラヒドロフラン(THF)、ピリジン、ジメチルアセトアミド、酸化メシチル、アセトン、塩化メチレン、クロロホルム、フェノール、2-ビロリゾン、ヘキサメチルホスホアミド、テトラメチル尿素等が挙げられる。これらの溶媒は用いる多糖誘導体の種類によって溶解性が異なるので、溶解性の良好な溶媒を選択して使用することになる。

【0015】本発明による光学分割方法は、上記のようにして得られた光学分割膜の片側に被分割化合物のラセミ体原液を接液させ、膜の反対側は空間としておき、膜内部に選択的に吸着された光学活性体を間欠的に洗浄液によって洗浄することによって、洗浄液中に光学活性体を回収する方法である。

【0016】本発明の方法により光学分割されるラセミ体原液としては、例えばノルマルヘキサン90%と2-ブロパノール10%の混合溶液に溶解させた、エチル-4-(2,2-パラシクロファニル)アクリレート、オクスブレノロール、アルブレノロール、ビンドロール、アテノール、トランスースチルベンオキシド、トレガー塩基等が挙げられる。本発明に用いられる洗浄液としては、例えば、ノルマルヘキサン-2-ブロパノール混合溶媒、ノルマルヘキサン-エタノール混合溶媒、エタノール水等が挙げられる。

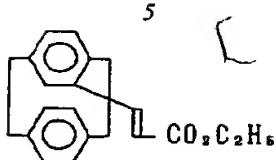
【0017】本発明は以下に記述する前実験において知見が得られ、発明のヒントになったものである。

## 前実験

セルローストリス(3,5-ジメチルフェニルカルバメート)300mgをTHF 10mlに溶解しドープを作った。このドープ中に直径30mmのテフロン製精密濾過膜を1時間浸漬したのち引き上げ、窒素気流中で1時間乾燥させて多糖誘導体固着膜を得た。得られた膜の光学活性体の選択吸着性を以下の方法で調べた。光学活性体の選択吸着性はシクロファンで総称される下記式で表されるエチル-4-(2,2-パラシクロファニル)アクリレートのラセミ体を試薬特級ノルマルヘキサン90%と2-ブロパノール10%の混合溶液に0.88mg/mlの濃度で溶解し、先に得られた膜を室温で4時間浸漬させたのち引き上げ、ノルマルヘキサン80%、2-ブロパノール20%の混合溶媒により膜中に吸着されたエチル-4-(2,2-パラシクロファニル)アクリレートの光学活性体を抽出し、液体クロマトグラフィー法で測定した。

## 【0018】

## 50 【化1】



【0019】分析に用いたカラムはダイセル化学工業製キラルセルODで流速 1.0ml/min、溶離液組成ノルマルヘキサン90%、2-ブロパノール10%、検出器UV ( $\lambda = 254\text{nm}$ )の条件で測定した。その結果、+体が光学純度72%eeを示したほか、溶離液をノルマルヘキサン95%、2-ブロパノール5%に代えた条件では+体が光学純度68%eeであることが判った。

#### 【0020】

【実施例】上記の前実験の知見は多糖誘導体を固着した膜により十分に選択的に光学活性体を得ることが可能である事を示しており、以下の実施例1～3によってより詳細に新規に発明された光学分割膜及びその膜を用いた光学分割方法を説明する。実施例1及び2における膜は基材膜を2枚合わせた膜を用いて行われたが、本発明は膜の貼り合わせは2枚に限定されるものではなく2枚以上の複数枚による分割効果向上が当然期待されるものである。実施例3に示される如く1枚膜によって行われる事も勿論可能である。本発明はこれらの実施例のみによって限定されるものではない。

#### 【0021】実施例1

多糖誘導体としてセルローストリス(3,5-ジメチルフェニルカルバメート)を用い、この200mgを試薬特級溶媒ジメチルアセトアミド15cc中に溶解してドープとした。このドープの中に住友電工(株)製、フルオロボア(登録商標、TYPE FP-045、ボアサイズ $0.45\mu\text{m}$ 、直徑25mm)2枚を約1時間室温で浸漬した。浸漬ドープ中から引き上げた膜は室温窒素気流中で1時間乾燥したのち、約1/10気圧に減圧されたデシケーター中で34時間乾燥した。更に膜中の不純物を除く目的で試薬特級ノルマルヘキサン90%、試薬特級2-ブロパノール10%の混合溶液中に室温で12時間浸漬してから約1/10気圧に減圧されたデシケーター中で4時間乾燥した。2枚の膜は上で用いたドープを接着剤として貼り合わせ1枚の膜とし、光学分割能を評価するために、図1の如きガラス製評価装置の中央に液密的に装着した。原液室4、透過室5の両方に試薬特級ノルマルヘキサン90%、試薬特級2-ブロパノール10%の混合溶液を満たし、膜3及びガラス製セル1の内部をよく洗浄した。試薬特級ノルマルヘキサン溶媒にエチル-4-(2,2-バラシクロファニル)アクリレートのラセミ体を $0.96\text{mg}/\text{ml}$ の濃度に溶解した液10mlと試薬特級2-ブロパノール1mlを、原液室4に入れた。原液はマグネティックスター-6によって攪拌された状態を保った。

【0022】数時間後、透過室5に洗浄溶媒として試薬特級ノルマルヘキサン及び試薬特級2-ブロパノールを

8:2に混合した液を0.2ml入れて、この洗浄液を用いて透過室側の膜面を約10秒間丹念に洗ったのち回収した。回収洗浄液中の光学活性体の測定はHPLC法で次の条件によって行われた。

カラム名；ダイセル化学工業製 キラルセルOD

溶離液；試薬特級ノルマルヘキサン80%、試薬特級2-ブロパノール20%

流速；1.0 ml/min

温度；室温

10 検出器；UV ( $\lambda = 254\text{nm}$ )

その結果は、エチル-4-(2,2-バラシクロファニル)アクリレートの+体の光学純度は24%eeであり、その回収量は0.03mgであった。更に数時間後、前回と同じ方法で透過室側に0.2mlの洗浄溶媒を入れて洗浄したところ、光学純度24%eeの+体を0.03mg得ることが出来た。

#### 【0023】比較例1

実施例1で使用した膜を用い、図1の装置の原液室4側に実施例2と全く同組成のエチル-4-(2,2-バラシクロファニル)アクリレートのラセミ体をノルマルヘキサン-2-ブロパノール(90:10)に溶解した液を入れた。一方、透過室5側には同時に実施例2で洗浄に用いたのと同組成の洗浄液を8ml入れて透過室側の膜面が常時洗浄液に接液している状態で数時間室温に放置した。透過室側の液を実施例1と同条件でHPLC法で測定したところ、光学純度はほぼ0%eeであり、光学活性体は回収されなかった。

#### 【0024】実施例2

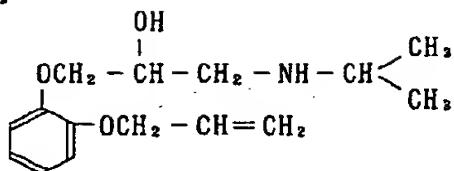
多糖誘導体としてセルローストリス(3,5-ジメチルフェニルカルバメート)を用い、その1gを試薬特級のTHF 30 9gに溶解してドープとした。このドープ中に実施例1で用いたテフロン製基材膜を2枚重ねて1時間浸漬した。この膜を引き上げ窒素気流中で1時間室温で乾燥させた後、約1/10気圧に減圧されたデシケーター中で4時間乾燥させた。乾燥された膜は試薬特級ノルマルヘキサン90%と試薬特級2-ブロパノール10%の混合溶液に12時間浸漬させたのち、1/10気圧に減圧されたデシケーター中で4時間乾燥した。

【0025】上で用いたドープを接着剤として二枚の膜を貼り合わせ、図1に示した装置に装着した。この際の

40 膜(有効膜面積 $3.14\text{cm}^2$ )中に固着されたセルローストリス(3,5-ジメチルフェニルカルバメート)の量は50mgであった。装置は30°Cの恒温槽に置き原液室4、透過室5の両方に試薬特級ノルマルヘキサン90%、試薬特級2-ブロパノール10%の混合溶液を満たし、膜及び装置系内をよく洗浄した。 $\beta$ -ブロッカとして医薬に用いられる下記式で表されるオクスピレノロールのラセミ体を試薬特級ノルマルヘキサン90%と試薬特級2-ブロパノール10%混合溶液に $1\text{mg}/\text{ml}$ の濃度に溶解し評価装置の原液室にその8mlを入れてマグネットスター-6で攪拌しながら数時間保持した。

【0026】

【化2】



【0027】透過室に試薬特級ノルマルヘキサン80%と試薬特級2-プロパノール20%の混合溶液0.2mlを入れ、この洗浄液でもって透過室側の膜面を30℃で10秒間よく洗浄することを10秒間隔で5回繰り返した。洗浄液の光学活性体は次の操作条件によるHPLC法によって測定した。

カラム名；ダイセル化学工業（株）製 キラルセルOD

溶離液；試薬特級ノルマルヘキサン80%、試薬特級2-\*

## オクスプレノロールの光学分割結果

	仕込み	残存原液 (実験値)	膜中残存物 (計算値)	透過物 (実験値)
量 (mg)	8	4.58	0.79	2.63
光学純度 (%ee)	0	+18	-23.4	-24.3

【0029】実施例3

多糖誘導体としてセルローストリス(3,5-ジメチルフェニルカルバメート)を用い、この100mgを試薬特級アセトン2g中に溶解してドープとした。このドープ中に直徑25mmの東洋漉紙(株)製 PO-200 限外漉過膜(素材；芳香族ポリアミド、公称分画分子量20,000)1枚を3時間室温で浸漬した。この膜を空气中で1時間乾燥後、1/10気圧に減圧されたデシケーター中で6時間乾燥した。膜中のセルローストリス(3,5-ジメチルフェニルカルバメート)の量は6mgであった。

【0030】このようにして得られた膜を図1に示した評価装置にセット(有効膜面積1.77cm<sup>2</sup>)し、恒温槽内で30℃に保持されたまま原液室4、透過室5の両室に試薬特級ノルマルヘキサン90%、試薬特級2-プロパノール※

## オクスプレノロールの光学分割結果

	仕込み	残存原液 (実験値)	膜中残存物 (計算値)	透過物 (実験値)
量 (mg)	10.0	4.05	4.19	1.76
光学純度 (%ee)	0	+5.6	+0.9	-14.5

【0032】光学純度の測定はHPLC法によって次の条件で行った。

カラム名；ダイセル化学工業（株）製 キラルセルOD  
溶離液；試薬特級ノルマルヘキサン：試薬特級2-プロ

9

パノール：試薬特級ジエチルアミン (80:20:0.1)

流速；1.0 ml/min

温度；室温

検出器；UV ( $\lambda = 254\text{nm}$ )

【0033】

【発明の効果】本発明のような膜分離法による光学活性体の分割は操作が容易であり、大容量処理に適している事から経済的な工業技術である。本発明は多糖誘導体等の光学分割能を有する物質を基材膜に固着させる方法によってつくられた膜を用いてラセミ体から直接光学活性体が分割される技術であり、更に新規な洗浄法によって光学活性体が簡単に得られるユニークな新技術である。

複雑な化学構造式を持つ $\beta$ プロッカ等の医農薬について

10

ても、本発明による膜分離法で直接分割によって光学活性体が得られる技術は画期的な事で産業上のメリットは大きい。

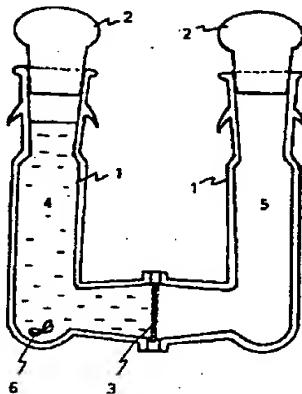
【図面の簡単な説明】

【図1】実施例及び比較例の実験に用いた光学分割能評価装置の断面図である。

【符号の説明】

- 1 ガラス製セル
- 2 擦合わせ共栓
- 3 膜
- 4 原液室
- 5 透過室
- 6 マグネティックスター

【図1】



# PATENT ABSTRACTS OF JAPAN

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(71)Applicant : DAICEL CHEM IND LTD

(22)Date of filing : 28.02.1992

(72)Inventor : OKAMOTO YOSHIO

YASHIMA EIJI

## (54) OPTICAL SPLITTING MEMBRANE AND OPTICAL SPLITTING METHOD WITH THE SAME

### (57)Abstract:

PURPOSE: To obtain an optically active material suitable for treatment in a large amt. with a simple operation by using an optical splitting membrane for which a material having a function for optical splitting ability such as polysaccharide deriv. is fixed to the inside and both surfaces of a base membrane and bringing a racemic compound source solution into contact with the one surface of the membrane film and then washing the other surface of the membrane with a washing solution.

CONSTITUTION: A material having the optical splitting ability such as polysaccharide deriv. of  $\beta$ -1,4-glucan (cellulose) is dissolved in an org. solvent, and then applied on the base membrane such as ultrafiltration membrane or precision filtration membrane by coating or immersing to be fixed to the inside and both surfaces of the base membrane. A racemic compound source solution being a compound to be split is brought into contact with the one surface of the obtd. optical splitting membrane, while the other surface of the membrane is maintained as vacant. The membrane is intermittently washed with the washing solution so that the optically active material selectively adsorbed to the inside of the membrane is recovered in the washing solution.

### LEGAL STATUS

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[Date of extinction of right]

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3. In the drawings, any words are not translated.

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CLAIMS

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[Claim(s)]

[Claim 1] The optical-resolution film which makes the interior and both sides of a base-material film come to fix the matter which has optical-resolution ability.

[Claim 2] The optical-resolution film according to claim 1 whose matter which has optical-resolution ability is a polysaccharide derivative.

[Claim 3] The optical-resolution method characterized by obtaining the optically active substance by washing other sides by the penetrant remover after contacting a racemic-modification undiluted solution on one side of an optical-resolution film according to claim 1 or 2.

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[Translation done.]

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## DETAILED DESCRIPTION

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### [Detailed Description of the Invention]

#### [0001]

[Industrial Application] this invention relates to the optical-resolution method which used the film for division and film of an optical isomer. It is related with anti-arrhythmia, anti-angina, a hypotensive agent, and the new film which enables division efficient also to the optical resolution of beta-blockers applied to glaucomatous treatment and the optical-resolution method using the film especially as present physic.

#### [0002]

[Description of the Prior Art] The importance of the optically active substance is increasing increasingly with progress of research and development in fields, such as medical drugs and agricultural chemicals, perfume, a seasoning, and liquid crystal. Especially in a life process, the optically active substance carries out unique work, and it is known that the thing of the physiological activity up optically active substance acquired on the other hand (D bodies, L bodies, + object, or - object) is very useful in many cases. The Ministry of Health and Welfare has indicated the 1985 edition drug manufacture indicator when the medicine concerned is racemic modification, it is "desirable" to examine absorption, a distribution, metabolism, and an excretion moving state about each isomer.

[0003] As the industrial technique which obtains the optically active substance from racemic modification, there are the diastereomer method, the priority crystallizing method, enzymatic process, a chromatography method, etc. now. After refining the diastereomer method by making optical activity acid or base (division agent) act on racemic modification, performing fractional crystallization using the difference of the solubility of the generated diastereomeric salt, and performing recrystallization, it is a method of obtaining the optically active substance, by decomposing by chemical preparation. In this method, the difficulty of the division agent selection by division agents having to be racemic modification and the thing in which a salt or a derivative is formed easily accompanies. Furthermore, a solubility difference is small, or optical resolution is impossible when there is nothing. moreover, it is also difficult to obtain the optically active substance of a high grade -- etc. -- it has the trouble

[0004] The priority crystallizing method is the method of adding the pure crystal of one antipode to the supersaturated solution of racemic modification as a seed, growing up alternatively only the crystal of this and an antipode of the same kind, and depositing. In spite of being the method which was very excellent, since the following technical problems occur, it is the actual condition which is hard to be referred to as being utilized broadly. That is, in order to divide a certain racemic modification by the priority crystallizing method, it is necessary to measure the solubility of racemic modification and both activators first, and to check in advance that it is a racemic-modification > activator and that the activator of the melting point is higher than racemic modification, that an activator does not dissolve in the saturated solution of racemic modification further, etc. (Yamanaka \*\*, Yasuhisa Tashiro, a quarterly issue chemistry total theory, No.6, 1989, and 4-5 pages).

[0005] Although the optical-resolution method using an enzyme can be classified to "bacterial coupling" and "enzymatic process", since an enzyme is a kind of dissymmetry molecule which

L-amino acid carried out peptide linkage and was able to do it, in many cases, a reaction advances as an asymmetric reaction. That is, since the enzyme itself has selectivity advanced as a catalyst, the industrial IE of D-amino acid by the enzymatic process which is used at the place of production of the optically active substance, and is suitable as a method of obtaining the optically active substance in large quantities, for example, combined the HIDANTOINAZE reaction and the chemical \*\* carbamoylation reaction has been established [S.TAKAHASHI, "Biotechnology of Aminoacid Production", H.YAMADA et al (eds), and Kodansha Ltd.(1986) p269]. Moreover, U.S. patent 4,800,162nd In the number, an enzyme is fixed in a polyacrylonitrile system hollow fiber, and the method of obtaining the optically active substance is indicated. However, the trouble in enzymatic process is that it is very difficult to find the enzyme which suits a racemic compound to carry out optical resolution.

[0006] A chromatography method is the method of making a stationary phase, using a chiral compound as a bulking agent, and separating using the difference of a distribution of the mobile phase by the interaction with the optical isomer in a mobile phase. Although it had resulted in the situation that quite a lot of preparative isolation is also performed while development of the latest bulking agent for HPLC (high performance chromatography) has a remarkable thing and Kamiichi of many columns for optical resolution was carried out, it just told that it was not quite satisfactory the region economically performed on a scale of industrial.

[0007] On the other hand, ignited by the membrane-separation method having accomplished progress with the ED of the reverse osmosis membrane which aims at seawater desalination fast about 30 years ago, ED is furthered mostly in parallel, the so-called artificial membrane is established as practical use technology, and the micro filter and the ultrafiltration membrane are also utilized in all industrial fields, such as physic, electronic industry, and an automobile. based on the principle of molecular sieving using the relative difference of molecule size and a membranous aperture, separation performs these films fundamentally — having — \*\*\*\* — an optical isomer — like — molecular weight — the same — although physical characteristics do not differ, either, it is well-known that it is completely chemical and unsuitable for separation

[0008] The features of a membrane-separation method are that separation cost is suitable for a lot of processing, and cheap. Therefore, development of the film suitable for optical resolution and development of the technology of mastering the film well are to demand greatly. If especially divided racemic modification can be divided without chemical modification into the optically active substance by the direct film method, it can be said that industrial worth of the technology is wonderful. That is, the method of separating the optically active substance using such a film is the new technology of conquering the peculiar fault which the above diastereomer methods, the priority crystallizing method, enzymatic process, a chromatography method, etc. have, respectively, and can expect that a lot of optically active substance is obtained economically.

[0009] About separation of the optically active substance using the film, the technology like the separation method (Japanese Patent Application No. No. 229743 [ two to ]) using the film which already introduces the optical activity matter into film material, and is obtained, and the separation method (Japanese Patent Application No. No. 334352 [ two to ]) using the film which consists of polymer which makes a polyamino acid with alpha-helical structure a constituent, the separation method (JP,63-57083,B) by the liquid membrane which made the crown compound hold to the micro filter made from polypropylene, etc. are known. However, no these are applied to separation of the physic in which it is a film for amino acid and a complicated chemical formula is shown. Therefore, the technical problem of this invention is to offer the film which can carry out optical resolution of the physic etc. efficiently, and the separation method using the film.

[0010]

[Means for Solving the Problem] That the above-mentioned technical problem should be solved, wholeheartedly, paying attention to the matter which has optical-resolution ability, such as a polysaccharide derivative already used abundantly in analysis and preparative isolation of an optical isomer at the column packing material of liquid chromatography, this invention person found out that the optical-resolution film which has good division ability was obtained, and completed this invention by fixing this to the interior and both sides of a base-material film, as a

result of research. That is, this invention offers the optical-resolution method characterized by obtaining the optically active substance by washing other sides by the penetrant remover, after contacting a racemic-modification undiluted solution on the optical-resolution film which makes the interior and both sides of a base-material film come to fix the matter which has optical-resolution ability, such as a polysaccharide derivative, and one side of this optical-resolution film.

[0011] Although there are a method of coating membranous one side or membranous both sides with this, a method immersed in a film into a dissolution dope after dissolving the matter which has optical-resolution ability in an organic solvent as a method of making the interior and both sides of a base-material film fixing the matter which has optical-resolution ability in this invention (it is called a dope), whichever it takes the method in the case of this invention, the effect does not change.

[0012] As matter which has the optical-resolution ability used for this invention, a polysaccharide derivative is desirable. A synthetic polysaccharide and a natural polysaccharide are not asked as a polysaccharide. For example, beta-1, 4-glucan (cellulose), alpha-1, 4-glucan (an amylose, amylopectin), alpha-1, 6-glucan (dextran), beta-1, 6-glucan (PUSUTSURAN), beta-1, 3-glucan, alpha-1, 3-glucan, beta-1, 2-glucan, beta-1, 4-galactan, beta-1, 4-mannan, alpha-1, 6-mannan, beta-1, 2-cell tongue (inulin), beta-1, 4-xylan, beta-1, 3-xylan, beta-1, 4-chitosan, a chitin, agarose, etc. are mentioned. Especially a desirable thing is a cellulose, an amylose, etc. from which the polysaccharide of a high grade is obtained easily. As a polysaccharide derivative used for this invention, there may be an ester derivative of the above-mentioned polysaccharide, a carbamate derivative, an ether derivative, etc., and you may be the any.

[0013] Moreover, as for the base-material film used for this invention, a ultrafiltration membrane, a micro filter, and a fine porous membrane may be used. If made from the material which is not dissolved in the solvent which are cellulose acetate, a cellulose nitrate, a regenerated cellulose, Teflon, polypropylene, polyethylene, the poly ape phone, polyether sulphone, polystyrene, a polyamide, a polyimide, a polyacrylonitrile, etc. as the material, and dissolves a divided compound, the film made from which material is also applicable.

[0014] Although a polysaccharide derivative is dissolved in an organic solvent and a dope is built in order to make a film fix a polysaccharide derivative, as a solvent used for it, a dimethylformamide (DMF), dimethyl sulfoxide (DMSO), a tetrahydrofuran (THF), a pyridine, a dimethylacetamide, an oxidization mesityl, an acetone, a methylene chloride, chloroform, a phenol, 2-PIRORIZON, a hexa methyl phospho amide, a tetramethylurea, etc. are mentioned. Since solubility changes with kinds of polysaccharide derivative to be used, these solvents will use a soluble good solvent, choosing it suitably.

[0015] It is the method of collecting the optically active substance in a penetrant remover, by making one side of the optical-resolution film obtained as mentioned above, as for the optical-resolution method by this invention, \*\*\*\* the racemic-modification undiluted solution of a divided compound, and the membranous opposite side's considering as space and washing intermittently the optically active substance by which the interior of a film was adsorbed alternatively by the penetrant remover.

[0016] As a racemic-modification undiluted solution by which optical resolution is carried out by the method of this invention, the ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate dissolved, for example in the mixed solution (normal-hexane 90% and 2-propanol 10%), an OKUSUPU leno roll, alprenolol, the pindolol, ATENORU, a transformer-stilbene oxide, a training gar base, etc. are mentioned. As a penetrant remover used for this invention, a normal-hexane-2-propanol mixed solvent, a normal-hexane-ethanol mixed solvent, ethanol water, etc. are mentioned, for example.

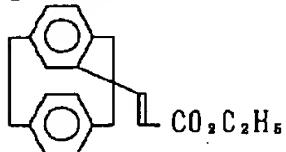
[0017] Knowledge is acquired in the pre-experiment described below, and this invention becomes the hint of invention.

Pre-experiment cellulose tris (3, 5-dimethylphenyl carbamate) 300mg It dissolved in THF 10ml and the dope was made. Pulled up, after the micro filter made from Teflon with a diameter of 30mm was immersed into this dope for 1 hour, and it was made to dry in a nitrogen air current for 1 hour, and the polysaccharide derivative fixing film was obtained. The selective-adsorption nature of the optically active substance of the obtained film was investigated by the following

methods. The selective-adsorption nature of the optically active substance dissolves racemic modification of the ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate expressed with the following formula named generically by the cyclophane by the concentration of 0.88mg/ml in a mixed solution (special-grade-chemical normal-hexane 90% and 2-propanol 10%). It pulls up, after making the film obtained previously immersed at a room temperature for 4 hours. Normal-hexane 80%, The optically active substance of the ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate by which the 2-propanol 20% mixed solvent adsorbed into the film was extracted, and it measured by the liquid chromatography method.

[0018]

[Formula 1]



[0019] The column used for analysis is the rate of flow at Chiralcel OD made from die cell chemistry. It measured on condition that Detector UV ( $\lambda=254\text{nm}$ ) 2-propanol 10% 1.0 ml/min and eluate composition normal-hexane 90%. Consequently, + object showed ee 72% of optical purity, and also it turns out that + object is ee 68% of optical purity on the conditions which replaced the eluate with to 2-propanol 5% normal-hexane 95%.

[0020]

[Example] The knowledge of the above-mentioned pre-experiment shows that it is possible to obtain the optically active substance alternatively enough with the film which fixed the polysaccharide derivative, and explains the optical-resolution film newly invented more by the detail according to the following examples 1-3, and the optical-resolution method using the film. Although the film in examples 1 and 2 was performed using the film with which two base-material films were aligned, membranous lamination is not limited to two sheets and, naturally, as for this invention, the improvement in the division effect by two or more two or more sheets is expected. Of course, it is also possible to be carried out with an one-sheet film, as shown in an example 3. this invention is not limited by only these examples.

[0021] as an example 1 polysaccharide derivative — cellulose tris (3, 5-dimethylphenyl carbamate) — using — this — 200mg — special-grade-chemical solvent dimethylacetamide 15cc — it dissolved in inside and considered as the dope The Sumitomo Electric Industries make and two fluoro pores (registered trademark, TYPE FP-045, and pore size 0.45micrometer, diameter of 25mm) were immersed at the room temperature into this dope for about 1 hour. The film pulled up out of the immersing dope was dried in the desiccator decompressed by about 1/10 atmospheric pressure for 34 hours, after drying in a room temperature nitrogen air current for 1 hour. Furthermore, after being immersed at the room temperature into the special-grade-chemical 2-propanol 10% mixed solvent special-grade-chemical normal-hexane 90% for 12 hours in order to remove the impurity in a film, it dried in the desiccator decompressed by about 1/10 atmospheric pressure for 4 hours. In order to use as the film of one lamination as adhesives the dope used in the top and to evaluate optical-resolution ability, it equipped with the film of two sheets in the center of the glass evaluation equipment like drawing 1 fluid-tight. The special-grade-chemical 2-propanol 10% mixed solution was filled special-grade-chemical normal-hexane 90% in both the undiluted solution room 4 and the transparency room 5, and the interior of a film 3 and the glass cell 1 was often washed. 10ml of liquid which dissolved racemic modification of ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate in the special-grade-chemical normal-hexane solvent at the concentration of 0.96mg/ml, and special-grade-chemical 2-propanol 1ml were put into the undiluted solution room 4. The undiluted solution maintained the state where it stirred with the magnetic stirrer 6.

[0022] Liquid which mixed a special-grade-chemical normal hexane and special-grade-chemical 2-propanol as a washing solvent in the transparency room 5 several hours after 8:2 0.2ml was put in, and it collected, after washing carefully the film surface by the side of a transparency

room for about 10 seconds using this penetrant remover. Measurement of the optically active substance in a recovery penetrant remover was performed by the following conditions by the HPLC method.

column name; — Daicel Chemical Industries make Chiralcel OD eluate; — special-grade-chemical normal-hexane 80% and special-grade-chemical 2-propanol 20% rate-of-flow; 1.0 ml/min temperature; room temperature detector; UV (lambda= 254nm) — for the result, the optical purity of + object of ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate was ee 24%, and the amount of recoveries was 0.03mg It is a transparency room side with the same method as several more hours after and last time. When the 0.2ml washing solvent was put in and washed, 0.03mg of + objects of ee was able to be acquired 24% of optical purity.

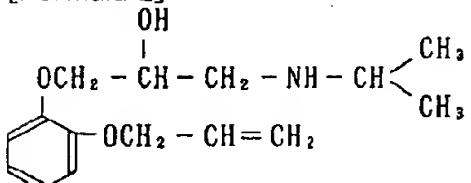
[0023] An example 2 and the liquid which completely dissolved racemic modification of the ethyl-4-(2 and 2-PARASHIKU loafer nil) acrylate of this composition in normal-hexane-2-propanol (90:10) were put into the undiluted solution room 4 side of the equipment of drawing 1 using the film used in the example of comparison 1 example 1. It was left in the room temperature for several hours in the state where, on the other hand, put 8ml of penetrant removers of having used for washing in the example 2 simultaneously, and this composition into the transparency room 5 side, and the film surface by the side of a transparency room is always \*\*\*\*(ing) to the penetrant remover. When the liquid by the side of a transparency room was measured by the HPLC method on an example 1 and these conditions, optical purity is ee about 0%, and the optically active substance was not collected.

[0024] Using cellulose tris (3, 5-dimethylphenyl carbamate) as an example 2 polysaccharide derivative, the 1g was dissolved in THF 9g of a special grade chemical, and it considered as the dope. Two sheets were immersed in piles for 1 hour in the base-material film made from Teflon used in the example 1 into this dope. After pulling up this film and making it dry at a room temperature in a nitrogen air current for 1 hour, it was made to dry in the desiccator decompressed by about 1/10 atmospheric pressure for 4 hours. After making the dried film immersed in a mixed solution (special-grade-chemical normal-hexane 90% and special-grade-chemical 2-propanol 10%) for 12 hours, it was dried in the desiccator decompressed by 1/10 atmospheric pressure for 4 hours.

[0025] The equipment which showed the film of two sheets to lamination and drawing 1 by using as adhesives the dope used in the top was equipped. The amount of the cellulose tris (3, 5-dimethylphenyl carbamate) which fixed in the film in this case (3.14cm of effective film surface products 2) was 50mg. Equipment was put on the 30-degree C thermostat, filled the special-grade-chemical 2-propanol 10% mixed solution special-grade-chemical normal-hexane 90% in both the undiluted solution room 4 and the transparency room 5, and often washed the inside of a film and an equipment system. It held for several hours, having dissolved racemic modification of the OKUSUPU leno roll expressed with the following formula used for physic as a beta-blocker at the concentration of 1mg/ml in special-grade-chemical normal-hexane 90% and the special-grade-chemical 2-propanol 10% mixed solution, having put the 8ml into the undiluted solution room of evaluation equipment, and stirring with a magnetic stirrer 6.

[0026]

[Formula 2]



[0027] It is 0.2ml (special-grade-chemical normal-hexane 80% and special-grade-chemical 2-propanol 20%) of mixed solutions to a transparency room. It repeated putting in, having by this penetrant remover and washing the film surface by the side of a transparency room with for [ sufficient ] 10 seconds at 30 degrees C 5 times at intervals of 10 seconds. The optically active substance of a penetrant remover was measured by the HPLC method by the following operating

condition.

column name; -- Daicel Chemical Industries, Ltd. make Chiralcel OD eluate; -- special-grade-chemical normal-hexane 80% and special-grade-chemical 2-propanol 20% and diethylamine 0.1% rate-of-flow; -- 1.0 ml/min temperature; -- room temperature detector; -- UV (lambda= 254nm) measurement result -- one of an OKUSUPU leno roll -- optical purity -- 12.2%ee -- 30microg It was obtained. the case where it washes by the completely same method at intervals of several more hours -- 25.6% of optical purity -- ee, 20.6%ee, 24.8%ee, and 23.6%ee -- one of an OKUSUPU leno roll -- 47.5microg, 55microg, 37.5microg, and 35microg It was obtained. change of some penetrant remover composition and a washing interval -- 12-hour place -- when a condition change of opening was made, the almost same result was obtained As a result of performing a total of 63 washing operations, the optical-resolution result as the last sum total became as it is shown in Table 1.

[0028]

[Table 1]

#### オクスピレノロールの光学分割結果

	仕込み	残存原液 (実験値)	膜中残存物 (計算値)	透 過 物 (実験値)
量 (mg)	8	4.58	0.79	2.63
光学純度 (%ee)	0	+18	-23.4	-24.3

[0029] Cellulose tris (3, 5-dimethylphenyl carbamate) is used as an example 3 polysaccharide derivative, and it is these 100mg. It dissolved into special-grade-chemical acetone 2g, and considered as the dope. It is the Toyo Roshi Kaisha, Ltd. make with a diameter of 25mm in this dope. PO-200 One ultrafiltration membrane (material; an aromatic polyamide, the nominal cut off molecular weight 20,000) was immersed at the room temperature for 3 hours. This film was dried for 6 hours in the desiccator decompressed by 1/10 atmospheric pressure after 1-hour dryness in air. The amount of the cellulose tris in a film (3, 5-dimethylphenyl carbamate) was 6mg.

[0030] Thus, it set in the evaluation equipment which showed the obtained film to drawing 1 (1.77cm of effective film surface products 2), and while it had been held within the thermostat at 30 degrees C, it filled up each both the loculus of the undiluted solution room 4 and the transparency room 5 with 10ml of special-grade-chemical 2-propanol 10% mixed solvents special-grade-chemical normal-hexane 90%. It was then left for 12 hours and a film and the whole evaluation equipment were often washed. The undiluted solution room 4 of the equipment after washing for optical-resolution ability evaluation was dissolved in special-grade-chemical normal-hexane 90% and 10ml of special-grade-chemical 2-propanol 10% mixed solvents, and OKUSUPU leno roll (beta-blocker) 10mg was put into it. Temperature was held at 30 degrees C. It is 0.5ml (special-grade-chemical normal-hexane 80% and special-grade-chemical 2-propanol 20%) of mixed solvents to the transparency room 5 side. It put in, the transparency side of a film 3 was washed for 1 minute, and the penetrant removers were collected. The completely same washing operation was repeated for every fixed time, and was performed 33 times, and the result of Table 2 was obtained.

[0031]

[Table 2]

オクスピレノロールの光学分割結果

	仕込み	残存原液 (実験値)	膜中残存物 (計算値)	透 過 物 (実験値)
量 (mg)	10.0	4.05	4.19	1.76
光学純度 (%ee)	0	+5.6	+0.9	-14.5

[0032] Measurement of optical purity was performed the following condition by the HPLC method.

column name; — Daicel Chemical Industries, Ltd. make Chiralcel OD eluate; -- special-grade-chemical normal-hexane: -- special-grade-chemical 2-propanol: -- special-grade-chemical diethylamine (80:20:0.1) rate-of-flow; -- 1.0 ml/min temperature; -- room temperature detector; -- UV (lambda= 254nm) [0033]

[Effect of the Invention] Division of the optically active substance by membrane-separation method like this invention is a technology it is [ operation ] easy and economical from being suitable for mass processing. this invention is the technology in which the direct optically active substance is divided from racemic modification using the film built by the method of making a base-material film fixing the matter which has optical-resolution ability, such as a polysaccharide derivative, and is the unique new technology in which the optically active substance is simply obtained by the still newer cleaning method. The merit on industry is large because the technology in which the optically active substance is obtained by direct division by the membrane-separation method by this invention also about medical drugs and agricultural chemicals, such as beta blocker with a complicated chemical structure formula, is epoch-making.

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[Translation done.]

\* NOTICES \*

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1. This document has been translated by computer. So the translation may not reflect the original precisely.
- 2.\*\*\*\* shows the word which can not be translated.
3. In the drawings, any words are not translated.

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DESCRIPTION OF DRAWINGS

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[Brief Description of the Drawings]

[Drawing 1] It is the cross section of the optical-resolution ability evaluation equipment used for the experiment of an example and the example of comparison.

[Description of Notations]

- 1 Glass Cell
- 2 Make it Rub and it is Stopper.
- 3 Film
- 4 Undiluted Solution Room
- 5 Transparency Room
- 6 Magnetic Stirrer

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[Translation done.]